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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,962	10/04/2004	Klaus Braun	4121-170	8435

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
PO BOX 14329
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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,962	BRAUN ET AL.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-27,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant Official Action is made in view of applicant's submission of 12/17/07. The submission of 12/17/07 has been entered and the finality of the previous Action has been withdrawn. The submission of 12/17/07, namely the amendments to the claims limiting the invention to "phage holin" has overcome the rejections of record. However the new rejection below provides prior art to address the phage-holin limitation. Any rejection made in the previous Official Action not repeated below is withdrawn.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-27, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nielsen et al [US 6,548,651], Good et al [Nature Biotechnology Vol. 19:360-364, 4/2001] and Rothbard et al [WO 98/52614], in view of Oki et al [Gene Vol. 197:137-145, 16 April 1997], Good et al (2)[Nature Biotechnology, Vol. 16:355-358], and Braun et al [US 6,821,948].

The claimed invention is as clearly set forth in the claims listed above. In general the invention is a PNA-transport conjugate comprised of a phage holing "transport protein and a PNA antigene oligonucleotide for the inhibition of bacterial gene expression.

Nielsen et al disclose modified PNA molecules that are conjugated to cationic peptides in order to enhance the anti-infective properties of the PNA. Neilson et al disclose that PNAs are advantageously used antisense compounds for microorganisms such as E. Coli (columns 4, 9, and 10, for example). At columns 1,2, 4, 8, and 9, and Example 5it is taught the use of PNA that binds to DNA including triplex embodiments. At column 4 it is stated that their invention relates to antisense oligonucleotides with the ability to bind to both DNA and RNA. At the top of column 9 it is taught that PNA2-DNA triple helix embodiments are clearly contemplated, for example. The general formula of peptide-linker-PNA is first disclosed at column 3, where the linker can be a linker or a chemical bond (see column 6, for example). At column 7 many peptides are disclosed including magainins which are antibacterial peptide, for example. It is taught at columns 6-7, the basic structure/requirements of the transport peptides that are contemplated for use in their invention. It is disclosed at column 4 that the compounds of their invention

can be used to inhibit infections by antibiotic resistant bacteria. At column 8 it is disclosed that the PNA is targeted to targets responsible for resistance to antibiotics and includes a gene encoding beta-lactamase that effect tolerance or susceptibility to ampicillin, for example, (column 9). Also at column 9 it has been taught that one should target antibiotic resistance genes with which the artisan is familiar and it is taught that such targeting could be used in antibiotic resistant bacteria. At column 8 many linkers are disclosed for use in their invention. At column 15 it is disclosed the combination of PNA conjugates and antibiotics for the treatment of infections including the use of PNA conjugates targeting genes responsible for resistance to antibiotics in combination with antibiotics..

Good et al have disclosed bactericidal peptide PNA conjugates. The conjugates comprise a peptide that that penetrates the cell membrane of E. coli and a PNA that inhibits *acpP* mRNA expression. The peptide and PNA are covalently linked. At page 361 Good et al assert that the E. coli outer cell wall is a major barrier to PNAs and that bacteria are permeabilized by cationic antimicrobial peptides and that such compounds can act synergistically with antimicrobials that enter cells poorly. Good et al tested whether such compound covalently attached to a PNA could further improve cell entry and found that indeed such antimicrobial peptides do indeed enhance PNA uptake into bacterial cells. Good et al teach the use of triplex oligonucleotides conjugated with transporter peptides at page 362.

Rothbard et al have taught general teaching for the construction of compounds that enhance transport across biological membranes. At page three it is taught that the

transport facilitator can be a peptide and at pages 4, 17, 21-22, and 34 for example, it is taught that biologically active agents such as PNAs can be facilitated across prokaryotic cell walls and membranes. At pages 4, 9, and 12-13 it is taught that various linkers such as cleavable linkers (including disulfide groups can be used to attach the transport moiety to the active agent. At page 26 it is disclosed the formulation of compounds with pharmaceutical carriers, for example. See also claims 13, 14, 15, 21, 22 and 24.

The prior art discussed so far has taught all of the limitations of the instant invention except the use of phage-holin peptides as transport mediators, the use of polylysine linkers, and the specific PNA sequence of claim 12.

Oki et al is relied upon to show that phage holin proteins were known in the art and known to be cell wall penetrating proteins and antimicrobial. The phage holin proteins clearly fall within that taught by Neilsen et al, Good et al and Rothbard et al as useful for transporting PNA compound across cell wall and or membranes. Phage holing proteins clearly belong to the genus of interchangeable transport proteins/peptides useful for transporting PNAs across cell walls/membranes. The instant specification provide no disclosure that phage holing peptides provide any more than what the prior art teaches one in the art to expect, namely transport function.

Good et al (2) is have taught the inhibition of beta-lactamase via PNA antisense molecules. It is noted that the antisense of Good et al is targeted to the beta-lactamase gene on the plasmid vector pBR322. The instant SEQ ID NO: 1 is also targeted to the beta-lactamase gene of pBR322. The sequence of SEQ ID NO: 1 was conveniently

chosen by applicant to perform the same known function of inhibiting the same beta-lactamase gene of pBR322.

Braun et al disclose the use of polylysine linkers in conjugates for cell membrane transport (see column 3, for example).

The prior art has clearly demonstrated the successful use of PNA molecules conjugated to cell penetrating moieties including bactericidal peptide transporter. Since the art has taught the benefit of such compositions and the prior art has taught that any bactericidal cationic peptide could be used, it would be obvious to choose any of the known bactericidal peptides known to permeate prokaryotic cell membranes (as was suggested by Good et al). The prior art provides a quantity of guidance on the choice of linkers one may choose or making the compounds of the invention (ie conjugates for cell membrane transport). One would clearly have been motivated to make the claimed conjugates since the prior art has made it abundantly clear that PNA activity is enhanced via the conjugation to cell membrane transporting moieties.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry
Primary Examiner
Art Unit 1635

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